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Topical Antibiotics in Cholecystectomy for Gallstone Diseases

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Summary

Efficacy of topical antibiotics in cholecystectomy for gallstone disease was evaluated. Forty-four patients who accepted topical single administration of 1 or 2 g each of latamoxef, cefmenoxime, cefotiam or cefamandole during operation were compared with 36 patients with systemic administration of cefem antibiotics by intravenous drip at a dose of 1 or 2 g, twice daily for postoperative 4 to 7 consecutive days.

In topical administration group, concentration of each antibiotic in the gallbladder and common duct bile, gallbladder tissue, parietal peritonea and intra- and postoperative peripheral blood exceeded mostly MIC_{80} against bacteria usually existing in bile by biliary tract infection or bacteria by wound infection. There was no difference between the two groups in postoperative clinical course.

Thus, an adequate prophylactic effect can be expected by topical use of antibiotic during cholecystectomy.

Introduction

Cholecystectomy for gallstone diseases is a most common operation in abdominal surgery. This operation is classified as semi-aseptic surgery in view of operative contamination[9], and in most cases, systemic administration of antibiotics has been continued for several days after operation for the purpose of prophylaxis of infections. However, some disadvantages of systemic antibiotics have already been pointed out[10] and therefore, the systemic administration can hardly be said to be an optimal prophylaxis of infections. In this study, we attempted to instill antibiotics topically during operation in patients who underwent cholecystectomy and were followed by no postoperetive systemic administration, and the results were compared with those obtained in control patients who also underwent cholecystectomy and received postoperative systemic administration of antibiotics to assess the usefulness of our topical use of antibiotics during operation.

Key words: Topical antibiotics, Cholecystectomy, Gallstone disease, Prophylaxis of postoperative infection, Systemic administration of antibiotics.

索引語：抗生剤局所投与，胆嚢摘出術，胆石症，術後感染予防，抗生剤全身投与.

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Materials and Methods

1. Subjects

Eighty patients with gallbladder stone who were admitted to the Department of Gastroenterological Surgery, Wakayama Medical College during a five-year period since 1985 were used in this study. In 36 patients who were hospitalized during the first two years, cephem antibiotics of second and third generation were systemically administered by intravenous drip at a dose of 1 to 2 g, twice daily in the morning and evening for four to seven consecutive days after operation, and they were used as control group. In 44 patients who were subsequently hospitalized, only topical administration of antibiotics during operation was performed: latamoxef (LMOX) in 11 patients, cefmenoxime (CMX) in 7, cefotiam (CTM) in 10, and cefamandole (CMD) in 16; they received no postoperative antibiotics treatment and were used as topical administration group.

No bile contamination in the operative field was noted in all patients of both groups, and when the abdomen was closed, drains were not put in the abdominal cavity.

2. Topical administration and dosage during operation

For topical administration, 1 g each of LMOX and CMX, and 2 g each of CTM and CMD were dissolved in 500 ml of physiological saline to prepare 2,000 μg/ml and 4,000 μg/ml of antibiotic solution, respectively. After the abdomen was opened, the operative field was developed by three sheets of gauze having a stick immersed with antibiotic solution (each of sticked gauzes containing 70 ml of the solution), and after 100 ml of the solution was spread in the field of operation, cholecystectomy was performed. Then, 50 ml of the solution was spread in the operative field. When the abdomen was closed, the subcutaneous tissues of abdominal walls were washed with 50 ml of the solution. The total doses of antibiotics used in these operative procedures were as follows: 820 mg of LMOX and CMX, and 1,640 mg of CTM and CMD.

These studies were approved by the human studies committee of the Wakayama Medical College and informed consent was obtained from each patient.

3. Testing items

1) Measurements of antibiotic concentrations

Measurements were carried out on the followings: blood obtained every 30 min after the start of operation, bile of gallbladder obtained by puncture of gallbladder immediately after cholecystectomy, bile of common bile duct obtained via tube inserted from cystic duct at intraoperative cholangiography, gallbladder tissues collected immediately after cholecystectomy, parietal peritonea obtained when the abdomen was closed, and blood collected twice every 60 min after the patient returned to his ward. The blood obtained was immediately separated into serum; a part of bile was put in an anaerobic specimen transporter (Kenki Porter^{R}, Clinical Supply Co. Ltd., Japan); gallbladder tissues and parietal peritonea were washed with physiological saline, and water was wiped up with gauze. After all these procedures, the samples were frozen and stored at $-20°C$ untill measurement. The concentration of each antibiotic in the samples was measured using high speed liquid chromatography. The antibiotic concentrations obtained were compared for MIC_{80} against various bacteria.

2) Bile culture

Bacteriology was done on bile placed in the anaerobic specimen transporter.

3) Clinical course

Febrile state after operation, changes in peripheral WBC counts, incidence of complications,

and hospital days after operation were compared between control group and topical administration group. For postoperative fever, thermometry was done four times a day and when the body temperature exceeded 37°C even once, the day was counted as a febrile day.

4. Statistical analysis

The results were expressed in mean±SD, and the significance of difference was analysed with Student's t-test.

Results

1. Concentrations of each antibiotic in the samples obtained during operation in topical administration group

1) Gallbladder bile and common bile duct bile (Fig. 1)

In both biles, the concentrations over MIC_{80} against gram-negative bacteria and anaerobes to be detected mainly in bile were obtained in three antibiotics-treated subgroups except the CMD-treated.

2) Gallbladder tissues and parietal peritonea (Fig. 2)

In both tissues, the antibiotic concentrations exceeded MIC_{80} in all groups treated with antibiotics.

2. Blood concentrations of antibiotics during and after operation in topical administration group (Fig. 3)

1) LMOX-treated subgroup

After the start of operation, the concentration gradually increased and showed a peak of 6.4 μg/ml 90 min later. After the operation, the antibiotic concentration was decreased with time, but it already exceeded MIC_{80} against gram-negative bacteria and anaerobes 30 min after the start of opera-

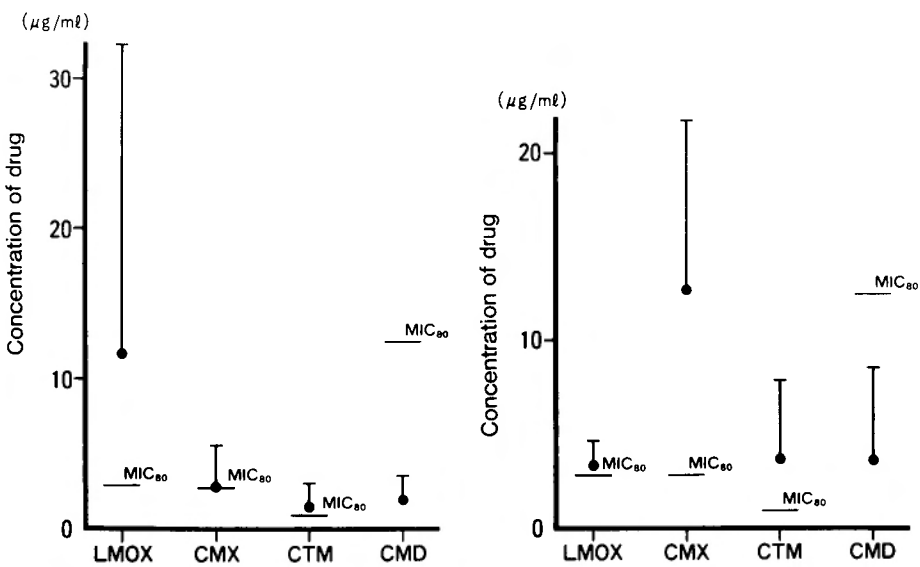

Fig. 1 Concentration of each antibiotic in gallbladder bile (left) and common bile duct bile (right). Each MIC_{80} means that against gram-negative bacteria and anaerobes.

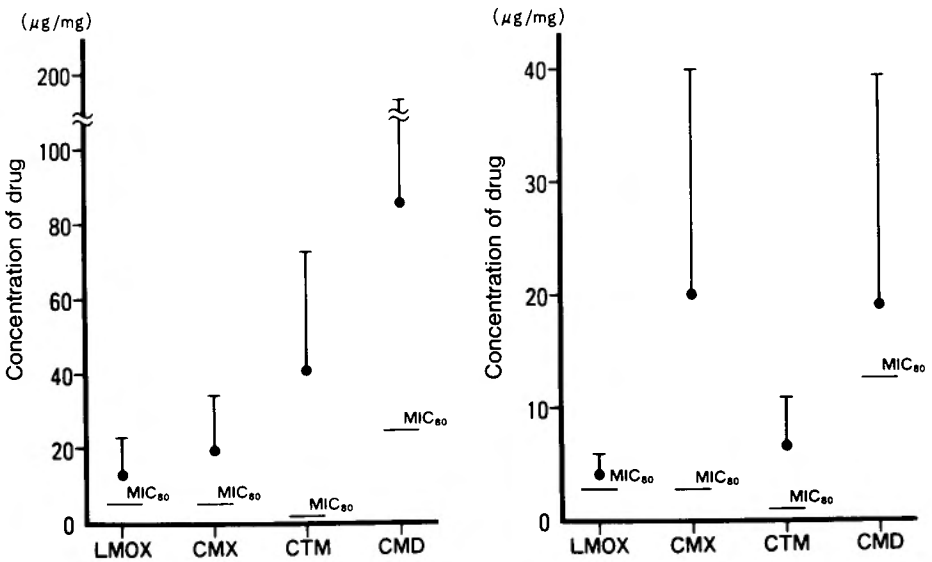

Fig. 2 Concentration of each antibiotic in gallbladder tissues (left) and parietal peritonea (right). Each MIC_{80} means that against gram-negative bacteria and anaerobes.

tion and only became lower than MIC_{80} 120 min after operation.

2) CMX-treated subgroup

The CMX concentration gradually increased after the start of operation and reached a peak

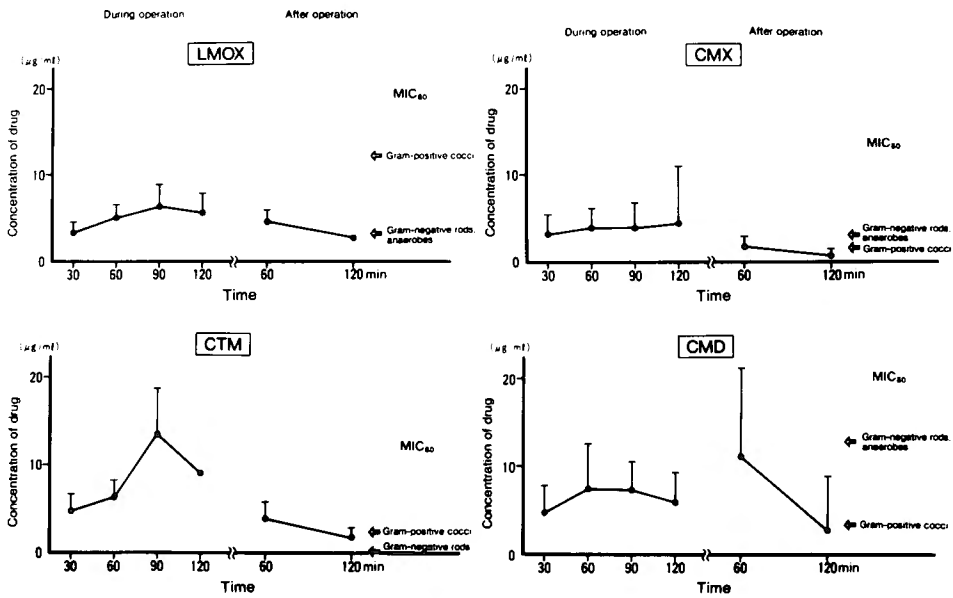

Fig. 3 Blood concentration of each antibiotic during and after operation in topical administration group.

Table 1 Comparison of postoperative maximal fever between two groups

Administration	No. of patients	Mean body temperature (°C)	Body temperature (°C)				
			<37	≦37.5	≦38.0	≦38.5	>38.5
Systemic	36	37.8±0.4		11	17	7	1
Topical							
LMOX	11	37.8±0.6	1	3	4	2	1
CMX	7	37.7±0.3		2	4	1	
CTM	10	37.5±0.2		7	3		
CMD	16	37.8±0.4		5	8	2	1

level of 4.4 μg/ml 120 min later. During operation, the concentrations exceeding MIC_{80} against gram-negative bacteria and anaerobes as well as gram-positive bacteria were maintained at each time point of blood sampling. After operation, only 60 min-values exceeded MIC_{80} against gram-positive bacteria.

3) CTM-treated subgroup

At 90 min after the start of operation, the concentration showed a peak value of 13.6 μg/ml exceeding MIC_{80} against both gram-negative and gram-positive bacteria. After operation, only 120 min-value became lower than MIC_{80} against gram-positive bacteria.

4) CMD-treated subgroup

Unlike the subgroups treated with three other antibiotics, the concentration of this antibiotic did not exceed MIC_{80} against gram-negative bacteria and anaerobes at any time points of blood sampling throughout the period during and after operation. Against gram-positive bacteria, the concentration exceeded MIC_{80}, except postoperative 120 min-value.

3. Comparison of postoperative clinical courses

1) Maximal fever after operation (Table 1)

Neither control nor topical administration group had the mean values exceeding 38°C and there was no significant difference between both groups. In the distribution of fever in individual cases, maximal fever over 38°C was seen in only one case from control group and two cases from topical administration group; both groups had no difference in the distribution state of fever.

2) "Febrile" days and "febrile" duration after operation (Table 2)

The number of febrile days in control group was 4.2 days on average, whereas it was relatively shorter in topical administration group; especially LMOX- and CTM-treated subgroups showed

Table 2 Comparison of postoperative fibrile days and fibrile duration

Administration	No. of patients	Mean fibrile days	Fibrile duration			
			2 days	4 days	6 days	8 days
Systemic	36	4.2±3.0	8	16	8	4
Topical						
LMOX	11	2.6±1.0*	4	7		
CMX	7	2.6±1.0	5	7		
CTM	10	1.9±1.0**	8	2		
CMD	16	3.0±1.3	5	9	2	

* $P<0.05$, ** $P<0.01$

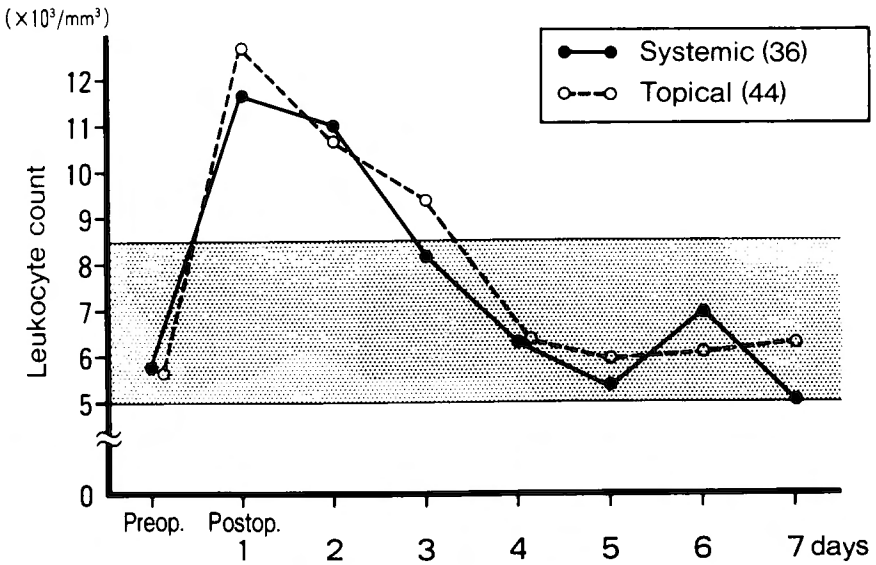

Fig. 4 Postoperative changes in leukocyte count. The shaded area shows the normal range.

earlier reduction to normal temperature. As for febrile duration, there were four cases which were febrile even after the lapse of eight days following operation in control group, whereas in topical administration group 42 cases except two recovered from feverishness within four days after operation.

3) Postoperative changes in WBC count (Fig. 4)

The WBC count was returned to normal range in three to four postoperative days in both groups, showing no difference between them.

4) Incidence of postoperative complication

The wound infection was not observed in both groups. As other complications, hepatic dysfunction was noted in two (5.6%) out of 36 cases of control group. In topical administration group, one (6.3%) out of 16 cases treated with CMD developed cystitis; this incidence results in one (2.3%) out of a total of 44 cases of topical administration group, thus showing no difference from control group.

5) Bacterial culture from bile collected during operation

In control group, bacteria were proved in six (19.4%) out of 31 cases. In topical administration group, bacteria were found in one (11.1%) out of nine LMOX-treated cases and in 3 (30%) out of 10

Table 3 Presence of bacteria in bile culture

Administration	No. of patients	No. of positive culture (%)	Bacteria detected
Systemic	31	6 (19.4)	E. coli, K. oxytoca, E. cloacae, E. faecalis, K. pneumoniae, S. epidermidis
Topical			
LMOX	9	1 (11.1)	K. oxytoca
CMX	6	0	
CTM	10	3 (30.0)	E. coli, E. faecalis, S. epidermidis
CMD	12	0	

CTM-treated cases; bacteria were not detected in the cases treated with CMX and CMD. The detected bacteria are shown in Table 3.

6) Postoperative hospital stay

The averaged number of hospital days was 12.3 days in control group while in topical administration group it was ranged from 10.2 days in CMD-treated subgroup to 11.8 days in LMOX-treated subgroup. There was no difference between both groups. As for postoperative hospital days, a peak was seen in a range from 10 days to 14 days in both groups. Two cases from control group which had more than 25 hospital days were those which postoperatively developed hepatic dysfunction.

Discussion

Surgical operation is classified by the degree of contamination of involved organs into three categories: 1) aseptic, 2) semi-aseptic and 3) contamination surgeries[9]. According to this classification, cholecystectomy for gallstone diseases belongs to semi-aseptic surgery.

For prophylactic administration of antibiotics after cholecystectomy, it has been generally accepted that antibiotics are systemically given by intravenous drip for several consecutive days[5]. However, it has also been pointed out that this administration method has the following disadvantages and problems[10]: 1) high incidence of side effects including hepatic and renal dysfunction, hypersensitivity, blood disorders and superinfection, and difficulty in treating them when occurred, 2) mental and physical restraint of the patient by intravenous drip for a long time[4], 3) difficulty to have the drug reach the target site and to maintain an adequate drug concentration there[2,15], and 4) economic problem in a broad sense such as expensive medical fee[6] or abundant urinary excretion of the drug administered[14]. Therefore, if the topical, single administration during operation attempted in the present study is proved useful for the prophylaxis of postoperative infection, it seems to be a good method which can solve major points of these disadvantages and problems.

The topical administration of antibiotics aiming at prophylaxis of postoperative infection has since been tried in some of the clinical fields[10–12,14]. According to study by SARR *et al.*[10], in which the prophylactic effects of only topical administration of antibiotics on postoperative infection were investigated in patients aged above 65 who underwent biliary tract operation, three groups of patients were treated with antibiotics as follows: first, 40 mg of neomycin and 2×10^8 units of polymyxin were dissolved in a solution of 1 *l*; in the first group, the peritoneal cavity was topically washed with this solution; in the second group, in addition to this topical treatment as in the first group, intravenous drip of 1 g of cefoxitin was given for pre- and postoperative three days; and in the third group, in addition to the same topical treatment as in the first group, three antibiotics of tobramycin, penicillin and clindamycin were administered for pre- and postoperative three days. In these three groups, the incidence of postoperative fever, wound infection, intraperitoneal abscess, urinary tract infection, pneumonia, and renal insufficiency was compared, and it was found that there was no difference between the three groups. The authors stressed the usefulness of topical administration of antibiotics especially in high risk cases of the aged.

As above, the topical administration of antibiotics in semi-aseptic operation has been accepted to be useful from the viewpoint of prophylaxis of postoperative infection, but the type of antibiotics and dosage are still controversial. GOLDBERG[3] described the experimental results that 25% solution of cephalothin was adhesive but not at less than 4%. Some types of antibiotics possess muscle relax-

ing action, and may have some unfavorable effects on respiratory muscle when administered intraperitoneally. This was considered to be due to neuromuscular blocking activity of antibiotics used during and after operation and a report of the first case was already made in 1956[8]. Antibiotics such as neomycin, streptomycin, kanamycin and colistin possess this activity[1]. Antibiotics without neuromuscular blocking activity should be selected for topical administration.

In the abdominal cavity, topical administration certainly makes it possible for antibiotics to reach the target site at a high concentration, and therefore it is a most useful method for the prophylaxis of local infection. Since, however, the purpose of antibiotic administration is to prevent postoperative infection, antibiotics must enter the circulation to exert a prophylactic effect of infection in other organs. Antibiotics administered intraperitoneally are rapidly absorbed to enter into blood circulation. By administration of four types of cephem antibiotics in the present study, similar results were obtained, and moreover, in many testing samples, the concentrations over MIC_{80} were obtained against bacteria usually existing in bile by biliary tract infection or bacteria by wound infection.

The effectiveness of antibiotics administered with a view to the prophylaxis of postoperative infection has been assessed not only by bacteriological examination of the treated area, but also by fever, peripheral WBC counts, WBC shift to the left of nuclei, CRP and ESR; in more details, by suppurative secretions, topical redness and febrile feeling or not in wound infection; by presence or absence of bacteria in catheter urine irrespective of clinical symptoms in urinary tract infection; and by clinical findings, X-ray findings, etc. in respiratory infection. With regard to fever, assessment was made with the number of days necessary for return to normal temperature. Besides this method of assessment on fever, there are other methods such as 1) febrile morbidity which compares the incidence of cases in which fever of 38°C was noted twice or more, excluding absorption fever for 24 hours after operation, by thermometry at 4 times a day[13], and 2) the method comparing fever index[7] which represents an area surrounded by a postoperative fever curve and a line of 37°C. In the present study, as one of the causes of more prolonged duration of fever in control group than in topical administration group, the occurrence of subclinical phlebitis associated with the insertion of a drip infusion needle cannot be denied.

As described above, when antibiotics are administered with the aim of prophylaxis of infection after cholecystectomy, while it is necessary to take into consideration the ability to reach each tissue and the antibacterial potency in selection of antibiotics, it is concluded that an adequate effect can be expected by topical, single administration during operation, only if bile contamination can be prevented in the operative field during operation.

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和文抄録

胆嚢摘出時の術後感染予防のための局所抗生剤投与

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胆嚢結石44例において術中術野に抗生剤を局所散布するのみとし，術後の抗生剤予防投与の必要性の有無を，同一手術で術後数日間第2，第3世代セフェム系抗生剤を全身投与した36例を対照に検討した．

LMOX, CMX は 1 g，CMD, CTM は 2 g をそれぞれ生食 500 ml に溶解し，開腹直後と閉腹前にこれらいずれかの抗生剤溶液を局所散布するのみとした．開腹直後から30分毎に採血，胆嚢摘出操作中に総胆管胆汁を，胆嚢摘出終了時に胆嚢胆汁と胆嚢壁組織を，閉腹時に腹壁腹膜を一部採取し抗生剤濃度を測定した．また帰室後1時間毎2回，血中濃度を測定した．LMOX 群，CTM 群，CMX 群では，各検体とも胆汁中検出菌の殆どの菌種に対し MIC_{80} 以上の有効濃度を示し，術後感染症も認めなかった．CMD 群では，胆汁および術中・術後の血中濃度で MIC_{80} を越える濃度は得られなかった．しかし臨床的には術後膀胱炎の発生を1例に認めたのみであった．これらの成績を対照群と比較した結果，術後の解熱日数，末梢血白血球数の推移，感染症発生率，入院日数とも差を認めなかった．

以上より，胆嚢摘出時の術野が胆汁汚染されなければ，術中の腹腔内・手術創抗生剤局所投与のみで十分な感染予防効果が期待できるといえる．しかしその際の抗生剤の選択は各組織への移行性と抗菌力に配慮する必要がある．